

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 30, 31, 33, 37-39 are now pending in this application, following the present amendments.

Claim 33 has been amended to more particularly point out and distinctly claim the invention. The amendments to the claim were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of the claim. Claims 37-39 are new, and they find support in the specification and claims as originally filed.

No new matter is added by these amendments.

Please replace the claims with the claims provided above.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Information Disclosure Statements

Applicants acknowledge receipt of the initialed PTO/SB0/8A forms submitted with the Information Disclosure Statements in this case, thereby indicating that the references cited therein have been reviewed and made of record.

Applicants respectfully request that the Examiner initial and return the PTO 1449 form submitted with the Information Disclosure Statement filed on herewith, thereby indicating that the reference cited therein has been reviewed and made of record.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 30, 31 and 33 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to enable one of skill in the art to make and use the invention commensurate in scope with these claims. Specifically, the Office Action asserts that while the specification is enabling for methods involving NS5B_{570, 544, 536 and 531}, the specification does not reasonable provide enablement for methods involving NS5B₅₇₀₋₅₃₁. The Applicants respectfully traverse this rejection.

The Office Action acknowledges that the Applicants have disclosed information to enable one

skilled in the art to perform the claimed methods involving NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁. Since new claims 37 and 38 recite methods that use only NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁, this rejection is believed to be moot with respect to these claims.

The rejected claims recite a genus of NS5B C-terminal deletion variants, and the specification provides exemplary working examples for at least four of those variants.

Procedures for examining claims to a genus when working examples are disclosed is discussed in the MPEP § 2164.02:

“Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.” As such, there is no *pro se* rule that an Applicant may only claim what they have shown in the working examples if a technology is unpredictable.

Regarding the enablement of a claimed genus, the MPEP states at §2164.02:

“For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.” As such, if a representative number of examples are shown in the specification, the claimed genus is considered enabled. There is no rule that states that every claimed species must be shown in the examples, even in an unpredictable art.

The subject claims are enabled by the instant specification

The Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the claimed invention without undue experimentation.

In making the rejection the Office states “it is unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to make others of predictable quality without undue experimentation” (emphasis added). The Applicants wish to again point out that **the Applicants provided information for four specific crystals**. Further, the Applicants wish to point out, as discussed on page 23 lines 8-17, that **NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁, were crystallized under identical conditions**. Since the same crystallization conditions were used for NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁, one of skill in the art would

instantly recognize that they could crystallize other deletion variants used in the claimed methods without undue experimentation. For example, since NS5B₅₃₁ and NS5B₅₃₆ were crystallized using the same method, one of skill in the art would expect to be able crystallize NS5B₅₃₂, NS5B₅₃₃, NS5B₅₃₄ and NS5B₅₃₅, using the same method. The same logic can be applied to the other deletion variants used in the subject methods. Why would one of skill in the art think that a new NS5B deletion variant, e.g. NS5B₅₃₈, which lies in the middle of the range of the working example NS5B deletion variants, would be only crystallizable under conditions different to those described in the specification? The Office has provided no rational evidence to answer this question, other than Drench, which addresses crystallization of a new polypeptide that has not already been crystallized and for which no methods are available. The Applicants respectfully submit that since so many of the claimed deletion variants are crystallizable using the same methods, one of skill in the art would expect to be able crystallize the genus of NS5B deletion derivatives of the subject claims without undue experimentation. In other words, the C-terminal deletion variants used in the subject claims are very similar to each other, and one of skill in the art would have no reason to think that they would not be crystallizable under the same conditions. In this respect, the Office should note that the C-terminus of NS5B, as shown in Figs. 1 and 2 of the instant application and in other art discussed in the response to the previous Office Action, is not embedded in the middle of the three dimensional structure of the folded NS5B protein. As such, one of skill in the art would recognize that changes to the C-terminus of the NS5B protein, such as a deletion or addition of a handful of residues, would not have any effect on the crystallization conditions of the protein.

The Applicants respectfully submit that they have crystallized examples (NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁) that are representative of the entire range of the genus of NS5B variants recited in the claims (NS5B₅₃₁₋₅₇₀). As such, the claimed methods should be considered enabled by the subject specification and the rejection may be withdrawn.

The foregoing discussion alone is sufficient for withdrawal of this rejection. To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

A recent publication has reported successful crystallization of other NS5B variants using the methods disclosed in the instant specification

This rejection hinges on the question of whether one of skill in the art could crystallize NS5B variants other than NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁ without undue experimentation. As discussed above, the subject patent application, on pages 22-23, provides a detailed method by which NS5B₅₄₄,

NS5B536 and NS5B531 may be crystallized. At question, therefore, is whether other not other these methods could be used to crystallize other NS5B variants.

The Applicants provide herewith a copy of a paper, published in the international peer-reviewed journal *Biochimica et Biophysica Acta* (volume 1601, pages 38-48, 2002) by Adachi et al. In this paper, Adachi reports crystallizing four NS5B variants, namely NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₅₂, using methods that are described in section 2.2.4, on page 40 of the paper. These methods involve crystallizing the NS5B variants in 5mM DTT, using 4-5% PEG 8000, 0.1 M sodium citrate, 5% isopropanol and 2.4 mM n-octanoylsucrose (a detergent). As such, the methods used in Adachi's paper are identical to the methods disclosed on page 22-23 of the subject specification, which describes a method involving crystallizing a NS5B variant in 5mM DTT, using 4-5% PEG 8000, 0.1 M sodium citrate and 5% isopropanol, with, as discussed on page 22 line 32, n-octanoylsucrose at 0.1-0.3CMC (critical micelle concentration).

Adachi et al. therefore uses a method that is identical to the method disclosed in the subject patent application to crystallize a NS5B variant other then NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁, namely NS5B₅₇₀, without undue experimentation.

As such, one of skill in the art would recognize, in view of Adachi's paper, that the methods described in the subject patent application could be used to crystallize NS5B variants other then NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₃₁, as described in the subject examples, without undue experimentation. Based on the methods set forth in the subject patent application, one of skill in the art would recognize that any of the NS5B variants recited in the claims, i.e. any one of NS5B₅₃₁₋₅₇₀, could be crystallized using the methods provided in the instant specification.

In summary, the Applicants respectfully submit that the four examples that they have provided are fully representative of the genus recited in the claims. Since representative examples have been provided, the claimed genus should be considered enabled. One of skill in the art would recognize the validity of these assertions because Adachi et al., by crystallizing NS5B₅₇₀, NS5B₅₄₄, NS5B₅₃₆ and NS5B₅₅₂ using the methods described on page 22-23 of the instant application, have substantiated those teachings. All one of skill in the art would have to do to crystallize any NS5B variant in the range of NS5B variants recited in the claims is to repeat the method recited on pages 22-23 of the subject specification. Considering a total of five representative NS5B variants in the claimed range have been crystallized using exactly the same method, why should one of skill in the art think anything differently?

The Applicants respectfully submit that one of skill in the art would consider the subject claims fully enabled by the specification. Accordingly this rejection of claims 30, 31 and 33 under 35 U.S.C. §112 first paragraph should be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph (new matter)

The Office has further rejected claim 33 under 35 U.S.C. §112, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office asserts that the lines 18 and 19, added by amendment in response to the previous Office Action, represents new matter.

Applicants respectfully submit that the above phrase does not represent new matter.

The requirement for written description involves the question of whether the subject matter of a claim conforms to the disclosure of an application as filed. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." (In re Gosteli, 872 F.2d 1008, 1012). The subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement (MPEP 2163.02). The mere inclusion of dictionary or art recognized definitions known at the time of filing would not be considered new matter (MPEP 2163.07(1)). Further, an application may incorporate the content of another document or part thereof by reference to the document in the text of the specification (MPEP 2163.07(b)).

The subject claim is supported by the specification in several places, as discussed in the response to the previous Office Action and in this Office Action. The Applicants respectfully submit that one of skill in the art would recognize that the Applicants had invented what is now claimed.

Nevertheless, solely to expedite prosecution, and without any acquiescence to this rejection, the Applicants have amended claim 33 to remove lines 18 and 19.

Applicants submit that they have more than met the requirements for written description in the subject patent application. Accordingly, this rejection of claim 33 under 35 U.S.C. § 112 should be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph (indefiniteness)

Claim 33 is rejected under 35 U.S.C. §112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action asserts that the limitation "the test agent" in line 19 has insufficient antecedent basis.

Applicants have cancelled lines 18 and 19 from claim 33 by amendment. As such, this rejection is believed to be moot.

Rejections under 35 U.S.C. §103

Claims 30, 31 and 33 are rejected under 35 U.S.C. §103 as obvious in view of Kim (USPN 6,183,121), *In re Gulack*¹ and Bressanelli (Proc. Natl. Acad. Sci. 96:13034-13039, 1999). Specifically, the Office Action asserts that Kim's method that uses atomic coordinates of an HCV NS3 helicase to generate a three-dimensional structure of a molecule comprising a NS3 helicase-like binding pocket, in view of Bressanelli's NS5B crystal structure, in further view of *In re Gulack*'s guidance as to the patentable weight of descriptive material, renders the subject claims obvious.

In order for a reference to be properly used as prior art under 35 U.S.C § 103 in the U.S., it must be published before the priority date of the application for patent in the U.S. The instant application was filed in the US on June 30, 2000, and claims priority to two Japanese patent applications JP11-188630 and JP11-192488, filed on July 2, 1999 and July 7, 1999, respectively.

The Bressanelli reference (published on November 9, 1999) is therefore published after the priority date of the instant application (July 2, 1999), and cannot qualify as a prior art reference under 35 U.S.C § 103.

As such, the instant invention cannot be made obvious over any combination of references that includes Bressanelli. Accordingly, Claims 30, 31 and 33 cannot be obvious under 35 U.S.C § 103 by Kim in view of Bressanelli and *In re Gulack*.

The Applicants respectfully submit that this rejection has been addressed and the rejection of claims 30, 31 and 33 under 35 U.S.C. §103 should be withdrawn.

¹ *In re Gulack* 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is earnestly requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number SHIM007.

Respectfully submitted,
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